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Bispectral Index Monitoring of Unihemispheric Effects in Dolphins

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When dolphins sleep, their electroencephalographic activity may change in only one cerebral hemisphere; i.e., the left and right brain hemispheres can take turns sleeping. We demonstrate that the bispectral index (BIS) monitor can detect interhemispheric asymmetry in the dolphin species *Tursiops truncatus*. Using two BIS sensors placed simultaneously over each side of the dolphin's head, we often, but not always, found significant differences between the two BIS values (e.g., left side 60 and right side 90) in non-medicated animals and in animals given propofol, atropine, and/or diazepam. Observations were each made over a period of approximately 3 h on dolphins resting out of the water. Unihemispheric effects may be inducible pharmacologically in dolphins. The dolphin, with its human-sized brain, may provide an animal model for study of unihemispheric effects in humans.

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The use of processed electroencephalogram (EEG) as a method of measuring the state of wakefulness during surgery has recently been simplified with the introduction of the bispectral index (BIS) monitor (Aspect Medical Systems) into anesthetic practice (1). Intraoperative utility of the BIS monitor has been controversial (2), as has the publication of studies reporting BIS values that are determined by its proprietary algorithm (3). Nevertheless, the robust design of the model A-2000™ “blue box” device encouraged us to consider its use as an indicator of the unihemispheric sleep previously reported to occur in dolphins (4). Although dolphins may have the most extreme form of unihemispheric sleep of which we are aware, the phenomenon has been described in other species, and has been found to be widespread in birds (5).

The goals of this study were to investigate whether the BIS monitor could:

1. Obtain a signal from a dolphin,
2. Detect EEG asymmetry between hemispheres in the species *Tursiops truncatus*

3. Distinguish a dolphin's natural, or drug-enhanced, sleep from wakefulness.

We hypothesized that the BIS monitor could do none of the above.

The second goal listed above was considered to have clinical relevance because recent studies have indicated that the BIS monitor may not detect unihemispheric effects in humans during carotid endarterectomy (6) or Wada testing (7). These reports were somewhat surprising because a weighted center of the bispectrum of the EEG has been used to sense hemispheric differences in rats with induced ischemia (8). If the BIS monitor could detect unihemispheric effects in an animal that has a brain size comparable to that of humans, then perhaps the dolphin may be a clinically interesting animal model for the study of focal cerebral effects.

METHODS

We evaluated this unusual use of the BIS anesthesia monitor as a possible indicator of unihemispheric “sleep” in support of a continuing research program at the SPAWAR Systems Center United States Navy Marine Mammal Program undertaken to understand brain physiology and improve health care for Atlantic bottlenose dolphins, *Tursiops truncatus*. The laboratory is accredited by the American Association for Accreditation of Laboratory Animal Care (AALAC), and these observations were conducted under protocols approved by the Institutional Animal Care and Utilization Committee of SPAWAR Systems Center, San Diego.

We initially placed a BIS Quatro™ electrode lead strip from a BISxp monitor on an animal trained to “beach” itself onto a mat adjacent to its ocean holding

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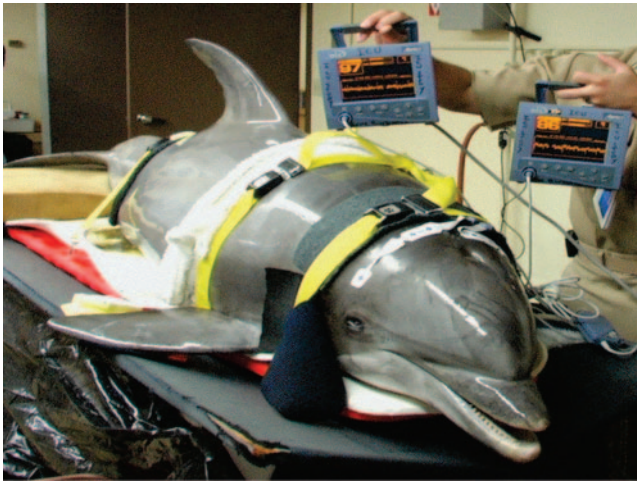


Figure 1. Photograph showing the montage of the bispectral index (BIS) monitor leads on a dolphin. Right BIS = 97, left BIS = 86. Narrow, tall spikes seen on the electroencephalogram displays are an electrocardiogram effect.

pen. The EEG signal was immediately detected by the monitor, good signal quality was indicated, and a BIS value in the high 90s was displayed. Subsequently, a dolphin, lying on a transport mat, was brought into a quiet room to investigate various lead placements. A report in the human literature indicated that placement of BIS monitor leads in positions different from those described by the manufacturer may still provide interpretable readings (9), and a statistically significant correlation of BIS values between frontal and occipital placement of electrode strips has been demonstrated (10). Empirically and pragmatically, we decided on the montage shown in Figure 1.

All measurements reported here were done on animals out of the water. All animals were part of long-term programs and were well conditioned to being handled and to lying on a mat in the laboratory as part of their normal clinical care. Observations using BIS monitors were taken incidental to their routine activity and continuing care. Seven different individual animals were monitored over the course of 18 mo. Data were recorded from 15 dedicated observational study times, each lasting approximately 3 h and starting at approximately 10 AM. The animals' electrocardiogram (ECG) and respiratory pattern were monitored continuously, and blood gases were occasionally measured. Staff veterinarians were present throughout the study times and used their clinical judgment to determine if an animal warranted intubation and respiratory support.

One group of investigators noted that diazepam can trigger unihemispheric slow wave sleep (11). Accordingly, we sometimes gave oral diazepam to the dolphins we were observing before they were "beached" out of the water.

To detect differences between the two hemispheres, two BIS monitors were used simultaneously. The lead strips were placed on each side of the dolphin's head, oriented vertically, with the end lead (#3) positioned

just above and behind the eye. This montage positions the leads in the closest proximity to the surface of the convexity of the cerebral cortex as a result of the minimal muscle tissue overlying the skull at this level. The BIS leads are then near locations where previously reported EEGs have been obtained on dolphins, using surgically implanted electrodes (12). The clocks on the two BIS monitors were synchronized. The BIS data were updated and stored every minute and were subsequently downloaded manually.

Signals were obtainable using standard BIS monitor leads with their packaged adhesive. We placed small subdermal needles through each lead (26- to 30-gauge, 1.25 to 2.5 cm) to stabilize the leads during the repeated "wetting down" of the surface of the animal by the attendants using water sprays.

When unequal values were displayed on the two monitors, the input leads were occasionally switched between the two devices to assure that the inequality was not attributable to any internal machine differences. Values would not be considered unequal unless the difference was substantially greater than the inpatient variability seen when using two BIS monitors simultaneously on a human patient (13).

The model A-2000 BIS Monitoring System™ monitors more than 1 EEG channel, and 2 EEG waveforms are obtainable from each hemisphere. These signals were captured and stored by a special data capture program written by one of the authors (JJF).

RESULTS

A representative set of simultaneously recorded EEGs is given in Figure 2 showing 6 s of captured EEG data from a nonmedicated dolphin and the calculated BIS for each side. The top part of Figure 2 shows the two EEG signal tracings obtained from the two channels over the right hemisphere. The middle part of the figure shows the two EEG signal tracings from the two channels over the left hemisphere, and the bottom part shows the corresponding BIS Index values that were displayed: right = 97 > left = 45. Note that the two EEG channel signal tracings from the A-2000™ BIS monitor can be displayed on the monitor's screen by first selecting the "Advanced Setup Menu," then "Display Parameter Setup," and then selecting "Dual EEG Display."

Of special note is the clear presence of larger amplitude ECG-like signals within EEG tracings shown in Figure 2. These large spikes correlated precisely with the independently monitored ECG and were seen in every dolphin and in both hemispheres but were seen only in one of the two EEG channels on each hemisphere. Presumably these "cardiac artifacts" were in the channel of electrodes 1–3 because we always saw it on the single EEG tracing that is shown when the monitor is not in "Dual EEG Display." In dolphins these cardiac waveforms were always asymmetric – the cardiac signal on the left hemisphere

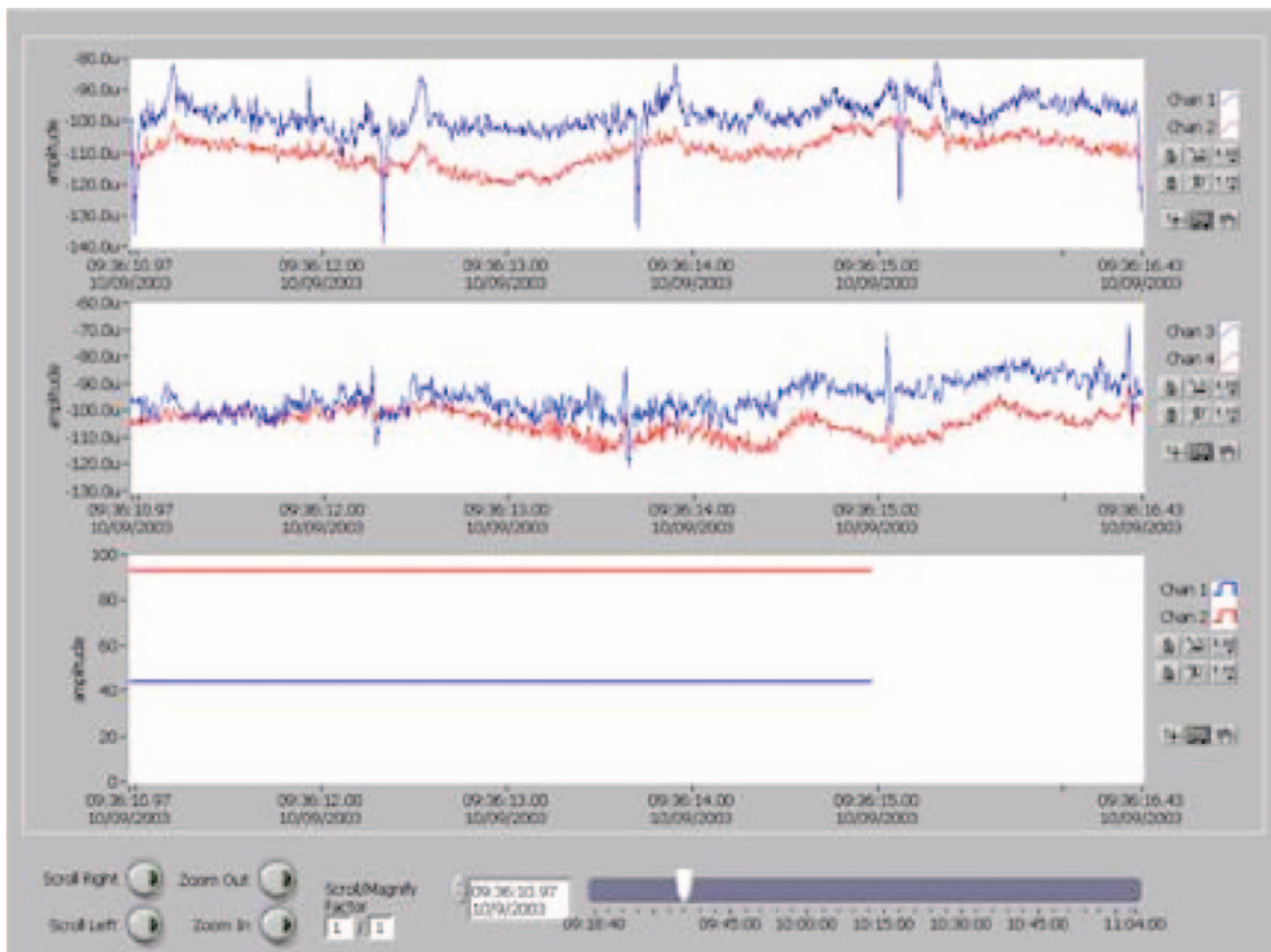


Figure 2. Display of 6 s of bispectral index (BIS) monitor data captured by specially written software, and measured on a non-medicated dolphin. The A-2000™ is a 2-channel electroencephalogram (EEG) monitor, and the two EEG tracings from the one monitor on the right side of the dolphin brain are shown in the upper section of the figure. The two simultaneously obtained EEG tracings from another monitor on the left side of the dolphin brain are shown in the middle section. The BIS readings associated with these EEG tracings are shown in the bottom section of the figure. In this case the right side monitor has calculated a BIS = 97 (awake) and the left side monitor has calculated a BIS = 45 (asleep).

monitor always showing both an up-and-down QRS spike and a purely downward spike always seen on the right hemisphere monitor. There may also be broadened upright T waves seen on either monitor and, because the cardiac frequency may be within that of expected “slow wave sleep,” there may be some cardiac interference with the processed EEG and so with the computed BIS. Nevertheless, despite these asymmetrical cardiac artifacts often both hemispheres would simultaneously display BIS values that remained in the high 90s throughout the several-hour observation period, and in one animal both hemispheres simultaneously displayed equivalently low BIS values after a sufficiently large dose of propofol was administered.

An outline of the results seen during the 15 dedicated observation periods is given in Table 1. The BIS values listed are representative values seen subsequent to any premedication given and then subsequent to any other drug given. Interhemispheric asymmetry in the readings was seen with and without

premedication. On two occasions the animal was tasked to whistle in response to unilateral visual stimuli being presented and showed no asymmetry during this.

Profound asymmetry was seen after administration of atropine on two occasions with one animal. This atropine effect was not seen on three occasions with two animals. One of these animals was twice given atropine and Valium and maintained high BIS values during the observation period; however, he was periodically responding to left and right visual stimuli by whistling. On the second occasion (Table 1, #5), after administration of 140 mg of diazepam followed by 4 mg of atropine and despite accurate responses to left and right visual stimuli with BIS values of 90 from both hemispheres, the dolphin was ataxic after being placed back in his bay enclosure. After receiving 2 mg of flumazenil IV, the animal resumed normal swimming.

On three occasions when propofol was given, the animals developed prolonged apnea and a loss of reflexes (e.g., corneal, menace) such that the attending

Table 1. Summary of Bispectral Index Values (BIS) Observed in *Tursiops truncatus*^a

No.	Name weight	PO premed valium dose	Drug given during observation	Subsequent BIS value		
				Left		Right
1	WEN♂ 185 kg	60 mg	None	~83	<	~97
2	LIS♀ 263 kg	30 mg	Atropine 4 mg IM Propofol 800 mg IV	~83 ~53 ~55	< < =	~97 ~91 ~56
3	LIS♀ 263 kg	40 mg	Atropine 4 mg IM	~90 ~55	= <	~88 ~80
4	NEM♂ 230 kg	80 mg	[Visual stimulation] Atropine 4 mg IM	~85 ~88	~ ~	~95 ~95
5	NEM♂ 230 kg	140 mg	[Visual stimulation] Atropine 5 mg IM	~90 ~90	= =	~90 ~90
6	BUG♂ 226 kg	60 mg	None	~85 ~85	> >	~70 ~70
7	FLP♂ 213 kg	80 mg	Atropine 4 mg IM	~97 ~70	~ <	~95 ~95
8	FLP♂ 213 kg	None	Propofol 400 mg IV	~70 ~45	< <	~90 ~90
9	FLP♂ 213 kg	None	Propofol 400 mg IV +200 mg 25 minutes later +200 mg 20 minutes later	~95 ~60 ~50 ~45	~ < < <	~90 ~90 ~80 ~90
10	WEN♂ 186 kg	None	Valium 100 mg IV	~90 ~89	= =	~95 ~94
11	BOE♀ 184 kg	None	Valium 60 mg IV	~60 ~60	< <	~90 ~90
12	NEH♂ 231 kg	120 mg	None	~95 ~95	= =	~95 ~95
13	NEH♂ 231 kg	None	Propofol 700 mg IV	~83 ~83	~ ~	~92 ~92
14	FLP♂ 212 kg	None	Propofol 1 gm IV	~80 ~40	< <	~95 ~85
15	BOE♀ 184 kg	60 mg	None	~80 ~95	< ~	~90 ~90

^aPremedications were given before having the dolphin jump out of the water. Later drugs were given with the animal resting on a mat in the laboratory. The first pair-set of bispectral index (BIS) values are representative values seen in the laboratory after only the premedication. The second pair-set of BIS values are representative values seen after the listed drug was given. The three pair-sets shown inside box borders were associated with prolonged apnea and loss of reflexes such that the animals were then intubated.

veterinarians decided that the animals warranted intubation. The associated BIS values on these occasions are shown on Table 1 inside box borders. The first occasion had bilaterally low BIS values, the second had bilaterally high BIS values, and the third had asymmetric BIS values. On each of these occasions the animals remained intubated for approximately 20 min.

A sample output of BIS trendlines is shown in Figure 3. In this example, asymmetrical BIS values, left < right, were observed before any pharmacologic intervention. Administration of 400 mg of IV propofol further depressed the left hemisphere readings and slightly affected the right hemisphere values.

In 9 of the 10 observational studies in which marked asymmetry of BIS values was seen, the left-side BIS values were lower than the right side. Whether this is a reflection of the asymmetrical cardiac artifact, or simply a result of some new, unsuspected, right-left hemispheric specialization, akin to the lateralization of the speech center in humans, is unknown.

DISCUSSION

BIS analysis is not the proprietary algorithm of Aspect Medical Systems. It is a standard, high-order statistical tool of time series analysis first introduced by oceanographers in the early 1960s to study nonlinearity in ocean wave height data (14). The traditional description of the bispectrum is that of a measure of interfrequency phase coupling. Because a correlation of cortical EEG bispectra with levels of consciousness may reflect phase-coherent synchronization over large spatial regions mediated by deeper brain structures, a proprietarily-calculated BIS might be independent of superficial unihemispheric effects. This may, in part, account for the initial reports of an inability of standard BIS monitoring to detect expected unihemispheric effects in humans undergoing carotid endarterectomy (6) or Wada testing (7). Statistical bispectral analysis of the EEG in rats that have had induced ischemia does indicate that interhemispheric asymmetry can be detected by EEG (8). Perhaps a simple reorientation of channel lead montage or a different, possibly higher-order, statistical analysis can be used

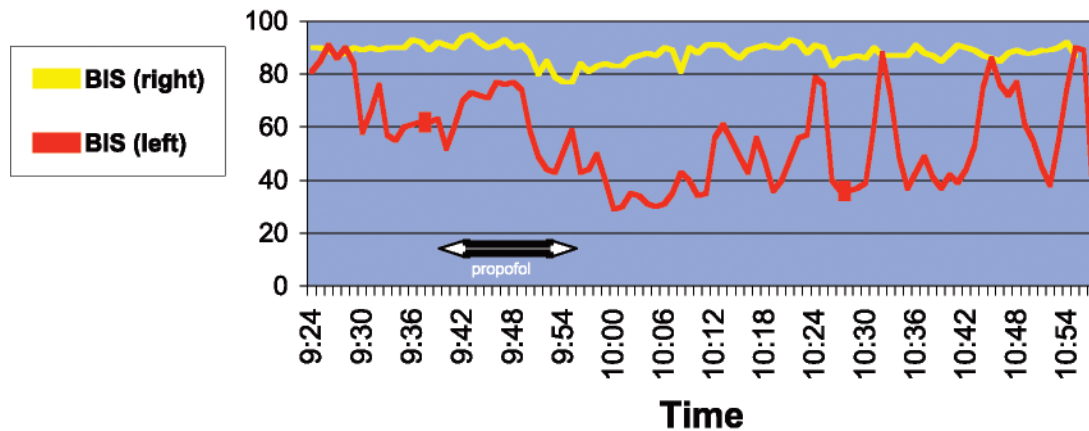


Figure 3. A sample output of the two unihemispheric trend lines of bispectral index (BIS) values observed in a 213-kg dolphin over a 1.5-h period. The left side showed profoundly lower values than the right.

to sense expected unihemispheric effects in humans. The present study suggests that the dolphin species *Tursiops truncatus* might be a particularly useful animal model for study of interhemispheric asymmetry in the EEG.

The use of the BIS monitor on nonhuman species has been reported in goats (15), horses (16), pigs (17), cats (18,19), and dogs (20–22). We have also obtained interpretable signals and BIS values using our monitors (model A-2000™) on juvenile elephant seals both during isoflurane anesthesia and during periods of unanesthetized sleep apnea, and on loggerhead and green sea turtles under medetomidine + ketamine anesthesia during experimental vision studies conducted at Hubbs-SeaWorld Research Institute in San Diego. The potential use of BIS monitoring in veterinary medicine has recently been reviewed (23), and the present study is the first report of its use on dolphins.

Cetaceans (whales, dolphins, porpoises) are mammals whose ancestors developed on land. Around 55 million years ago, these ancestors returned to the water and evolved a completely aquatic life which required a different style of breathing. Bottlenose dolphins, with which we work, have an apneustic style of breathing, considered to be under conscious control. They do not breathe spontaneously when under general anesthesia. Cetaceans have never been successfully anesthetized without complete respiratory control and positive pressure ventilation (24). Even when resting at the water surface, bottlenose dolphins ordinarily take only one to three breaths per minute, each breath consisting of a rapid, deep filling of the lung to 80% or 90% capacity. This effort of breathing, even at rest, appears much more pronounced and more deliberate than that of humans and other terrestrial mammals. Given their need to swim and breathe air with these deep respirations, it is not surprising that many have wondered how these mammals manage to sleep in the water.

In the early 1960s, John Lilly (25) suggested that bottlenose dolphins slept with one eye closed at a time

and with only one hemisphere at a time; however, he produced no EEG data to support the claim. The first EEG evidence of unihemispheric sleep was obtained in 1970 (26) using subcutaneous needle electrodes during a one-night recording on another member of the dolphin family, the pilot whale. Subsequently, other investigators (27) have recorded EEG data over 24-hour periods from many dolphins using electrodes inserted through the skull and connected to a tethered, or more recently, a portable (28) multichannel array that allowed animal movement within a shallow pool. They showed evidence that a significant majority of dolphin slow waves were unihemispheric, appearing first in one hemisphere and then in the other.

EEG activity may be the best evidence of hemispheric wakefulness. Extensive behavioral observations of dolphin sleep have been conducted by McCormick (29), who was able to observe bottlenose dolphins through large underwater viewing windows. He observed dolphins resting at the water surface, virtually immobile, with both eyes closed and breathing in an “automatic fashion” for periods of an hour or more. McCormick also observed that the Dall porpoise, *Phocoenoides dalli*, swam continuously without ever appearing to stop for rest or sleep. It would be easy to conclude that the Dall porpoise never sleeps. However, Azov porpoises, *Phocoena phocoena*, in the same family as the Dall porpoise, have been observed to swim continuously while EEG recordings from these animals still show unihemispheric slow waves alternating between the hemispheres during swimming (30). Thus stopping to rest or becoming immobile is not an absolute requirement for sleep. There is a recent report (31) of the mothers and calves of both bottlenose dolphins and killer whales swimming constantly for several weeks without apparent rest. If “sleep” is needed during this time, they may get it in the manner of an Azov porpoise, i.e., unihemispherically while swimming.

The human EEG changes during both sleep and anesthesia. The changes that are seen during sleep have been well described, with 4 “stages” defined

using EEG criteria (32). The EEG changes seen during drug-induced general anesthesia have not been as well defined, although there have been some published descriptions of the basic analytical techniques, presumably incorporated into the EEG processing done by the BIS monitor (33). The relationship, if any, between the EEG-defined 4 stages of human sleep and the commonly described 3 stages of anesthesia has not yet been quantitatively correlated. Nevertheless, a BIS value <80 has been reported to correspond to natural sleep (34), and a decreasing BIS value has been seen with increasing sleep depth (35). Other researchers have reported some correlation of BIS values with sleep stages (36).

The physiologic purpose for which general anesthesia was developed may be simpler, or at least more clearly understood by us, than the mysterious reasons why animals (including humans) ever developed a need for sleep (37). There may be no *a priori* reason to suspect that the EEG changes seen in these two disparate physiologic states of general anesthesia and normal sleep should be similar. So the basis of our trying, in the present study, to use a BIS anesthesia monitor to monitor sleep in dolphins was admittedly influenced more by our familiarity with this device in the operating room and by the apparent robust design of the monitor than by any anticipation that the EEG changes we expected to see during dolphin sleep would necessarily be similar to those we see when humans are anesthetized.

The ECG-like cardiac artifacts seen in every dolphin observed, although only on one of the two EEG channels displayable from each hemisphere, are puzzling. We are unable to explain why this apparent ECG effect is not seen on the other, nearby, EEG channel. We doubt that it is a pulse artifact because there are no nearby superficial arteries and the intracranial circulation in dolphins is effectively nonpulsatile, being supplied mainly by a massive thoracospinal retia, without a Circle of Willis (38). Similar ECG interference has sometimes, although not always, been seen in human patients by one of the authors (RSH) during surgery in the prone position with the BIS sensor leads placed over the occiput, and an "ECG artifact" in the BIS has been reported (39) in a human patient with severe ischemic brain injury.

Figure 3 shows wide oscillations of the left side BIS values over a period of minutes. This is different from the hour-long periods of unihemispheric EEG synchronization that have been reported for dolphins (4,11,12,28) and may represent a simple difference in signal processing speed and sampling now available in the BIS monitor, which is a near real-time monitor. The rapidity of the EEG changes we have observed might indicate that the underlying physiology of unihemispheric sleep may not be simply attributable to hemispherically independent control of the blood supply in the dolphin.

The BIS monitor or bispectral analysis of the EEG as a physiological measurement tool for use in other species may become an interesting application of a heretofore exclusively anesthetic technique. Although the "blue boxes" have not yet been demonstrated to be effective in monitoring expected unihemispheric effects in humans, they are evidently able to sense the unihemispheric daze of the dolphin.

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